NOTE

AUDITORY CEREBRAL LATERALIZATION FOLLOWING CROSS-GENDER HORMONE THERAPY

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Abstract

In this study, 10 men, 10 women, and 13 genetic male transsexuals, all of them right-handed, were tested on two verbal (CV and nonsense polysyllables) and two nonverbal (melodies and triple tone [3T]) dichotic tasks to investigate relations between hormone therapy and auditory cerebral specialization for speech and non speech stimuli in adults. At time of testing, all transsexuals had been under hormonal treatment for at least one year and eight had had corrective surgery. ANOVA results showed a right ear advantage and similar pattern of performance for the three groups in the treatment of speech. In nonverbal tasks, interactions revealed a left ear advantage in the processing of melodies and 3T for men only; women and transsexuals exhibited similar performance in both nonverbal tasks. In accord with generalization from the animal literature, cautious interpretation of the data is some possible hormonal involvement, in adults, in the modulation of right hemispheric cognitive processing.

Introduction

In recent decades, accumulated experimental evidence suggests that hormones play a major role in influencing cellular development during critical periods of early life. Correlations between variations and levels of gonadal steroid hormones and brain and behavior differences have been reported in the animal literature (Goy and McEwen, 1980; Diamond, Dowling and Johnson, 1981; MacLusky and Naftolin, 1981; Stewart and Kolb, 1988; Fitch, Berrebi, Cowell et al., 1990). Data in humans also suggest the existence of hormonal influences on development of the cortex (Taylor, 1969; Witelson, 1991), artistic talent (Hassler, 1991), spatial abilities (Shute, Pellegrino, Hubert et al., 1983) and a large body of research has been directed at the investigation of hemispheric functional asymmetries (see McGlone, 1980; Bryden, 1982; Geschwind and Galaburda, 1987). There is substantial evidence that the pattern of cerebral performance asymmetry is different for each sex (McGlone, 1986; Kimura, 1992) with men showing greater lateralization than do women for some aspects of verbal and spatial processing. But many studies have failed to find differences between men and women in cerebral function asymmetries (Fairweather, 1976) and the hypothesis of a modulation of sex hormones on cognitive abilities in humans has been seen as conjectural by some researchers (e.g., Cappa, Guariglia, Papagno et al., 1982).

Nevertheless, the relationship between levels of gonadal hormones and sex differences in behavior and brain suggest that the early hormonal environment plays an important role in the establishment of these differences. Behavioral data from individuals with congenital hyperplasia (CAH) exposed to adrenal-derive androgens (Resnick, Berenbaum, Gottesman et al., 1986; see also Nass and Baker, 1991), and others whose mothers were treated during pregnancy with hormones such as the synthetic estrogen diethylstilbestrol (DES; Hines and Shipley, 1984) support this possibility. Other studies also suggest that sex hormones may be involved in the development of human cerebral functional asymmetries. Reduced or reversed ear asymmetries on dichotic tasks were obtained in studies of women with Turner

syndrome (Gordon and Galatzer, 1980). Pre- and postnatal deficit in estrogen and progesterone is a major characteristic of Turner syndrome (Singh and Carr, 1966) and the unusual asymmetry could therefore be due to low level of gonadal hormones during development. Males with similar types of disorders, such as Klinefelter's syndrome with low levels of testosterone (Netley and Rovet, 1984; Braun, 1988) and idiopathic hypogonadotropic hypogonadism (e.g., Hier and Crowley, 1982) also show atypical patterns of cognition of functional asymmetry. Individuals with Turner's or Klinefelter's syndrome, however, have disorders of the sex chromosomes that may explain the unusual lateralization patterns (e.g., Netley, 1988; Netley and Rovet, 1987).

Geschwind has theorized that a relation between patterns of cognitive function and hormone effects may be at the level of cerebral lateralization (Geschwind and Galaburda, 1985). In this study, testosterone both plays a determining role in the early development of cortical asymmetry and may itself be modulated by genetic variants associated with the major histocompatibility complex (Geschwind and Behan, 1982). A relative increase of testosterone during the developmental period would also produce a slower growth of the left hemisphere, resulting in anomalous pattern of hemispheric asymmetries.

In addition to the apparent contribution of the prenatal hormonal environment on laterality patterns, one of the most intriguing findings is that cognitive patterns may remain sensitive to hormonal fluctuation throughout life. Some structures in the CNS appear to remain plastic well into adulthood, modifiable not only as a result of learning and experience, but also in response to the influence of gonadal hormones (Greenough, 1986; Forget and Cohen, 1994).

In a study comparing pre- and postmenstrual dichotic performance, the right ear advantage (REA) obtained for auditory stimuli was significantly more pronounced in the postmenstrual phase of the cycle (Altemus, Wexler and Boulis, 1989). Changes over the menstrual cycle were also observed on visual cerebral asymmetries in a lexical decision task (Chiarello, McMahon and Schaefer, 1989). Moreover, shift of functional cerebral asymmetry in face perception also accompanied variations in the menstrual cycle (Heister, Landis, Regard et al., 1989).

The interest in biological origins of brain hemispheric asymmetries makes the question of the invariance of these hormonal influences an important one. Namely, is it the case that these influences on laterality are a function of a given hormonal state, independently of genetic sex, and that sensitivity of hormones in adults is not irrevocably designated in the perinatal brain? The study of hemispheric cerebral specialization in individuals who have been accepted for cross-gender role reassignment provide an opportunity to test whether patterns of asymmetry are genetic sex-specific or influenced by hormonal environment.

In this perspective, the aim of the present study was to determine to what extent differences in performance in verbal and nonverbal dichotic listening tasks emerged when the nature of the hormonal environment is considered. Individuals who had undergone sex corrective surgery (biological males to females) or were under cross-gender hormonal treatment for at least one year participated in this study and were compared to reference groups of men and women. More specifically, to the extent that men and women show different patterns of hemispheric specialization, the observation that genetic male transsexuals and men show different patterns of auditory lateralization — or that genetic male transsexuals and women exhibit similar patterns of auditory lateralization — would add support to the hypothesis that neuroendocrine influences in the modulation of functional brain asymmetry are not necessarily determined in the perinatal brain.

Materials and Method

Subjets

Thirteen genetic male transsexuals who had been accepted for female role reassignment participated in this study. These subjects were part of an ongoing long-term followup design investigating sexual and psychological adjustment following cross-gender reassignment. The genetic male transsexuals had been under continuous cross-gender hormonal treatment for at least one year (range = 1.3 to 23.8 yr) to stimulate female secondary sex characteristics

TABLE I
Hormonal Correction and Duration of Therapy

Transsexual subjects	Hormonal therapy (at time of testing)		Duration of HT (in years)	Surgery*
1	Estinyl	(0.5 mg/d)	2.3	0.5
	Provera	(10 mg/d @ last 10 d/m)		
2	Estinyl	(1.0 mg/d)	1.3	
3	Tace	(12 mg/d)	4.8	
	Delalutin	(1.5 cc/wk)		
	Delostrogen	(1.5 cc/wk)		
	Cebestrole	(5 mg/d)		
4	Estinyl	(0.5 mg(d)	4.2	
	Tace	(72 mg/d)		
5	Provera	(10 mg/d)	1.8	
	Premarine	(5 mg/d)		
6	Estinyl	(0.5 mg/d @ 20 d/m)	12.9	
	Provera	(10 mg/d @ last 10 d/m)		
7	Premarine	(0.625 mg/d)	20.0	1.0
8	Delalutin	(1.5 cc/m)	23.8	8.9
	Delostrogene	(1.5 cc/m)		
9	No therapy at time of testing		17.0	13.0
10	No therapy at time of testing		7.5	6.0
11	Estinyl	(0.5 mg/d)	7.0	4.0
12	No therapy at time of testing		13.0	6.0
13	Delalutin	(2 cc/21 d)	13.8	12.5
	Delostrogene	(4 cc/m)		

* Time elapsed (in years), at time of testing, since radical genital surgery.

and, at time of testing, eight had had radical genital surgery. Transsexual subjects were aged 22-50 (mean age = 34.6 years) and had 10-21 years of education (mean level of education = 13 yr). Except for drugs taken in the course of hormonal therapy (see Table I), the transsexual subjects were free of medication at time of testing. Ten men and 10 women were recruited from the university community to serve as reference groups (mean age = 32 years; mean level of educations = 14 yr). All subjects were native speakers of Canadian French, were without a history of neurological problems, were right-handed on the Edinburgh Inventory (Oldfield, 1971), and reported no hearing deficit.

Stimulus Materials

Two verbal and two non-verbal sets of dichotic stimuli were used in this study. Tokens of the six CV syllable /ba/, /pa/, /da/, /ta/, /ga/, /ka/ were spoken by a male phonetician and then digitized, edited to a common duration of 350 msec, and stored on a computer tape. A dichotic tape of 30 possible pairs was made by calling up pairs of these CV stimuli with 0 msec onset asynchrony and reconverting them to analog form. A set of 123 pairs of trisyllabic nonsense stimuli (e.g., *logador — lopapor*) made up the second set of speech stimuli. Twenty four pairs of melodies, similar to those used by Kimura (1964), and 123 pairs of triple tones (3T) made up the non-verbal sets of stimuli. Triple tones were composed of three 500 msec long simple frequency bursts in the range between 200 Hz and 4000 Hz.

Procedure

All subjects were tested singly in a sound-proofed room. A Sony TCD-SM tape recorder and Sennheiser headphones were used for the presentation of all dichotic material. Order of presentation of the sets of dichotic stimuli was counterbalanced across subjects. Channel of stimulation was also counterbalanced; earphones were reversed after half of the trials in the CV and melody stimulation conditions. There were two presentations of the set of CV speech stimuli. In the case of nonsense polysyllables and 3T presentations, subjects were required

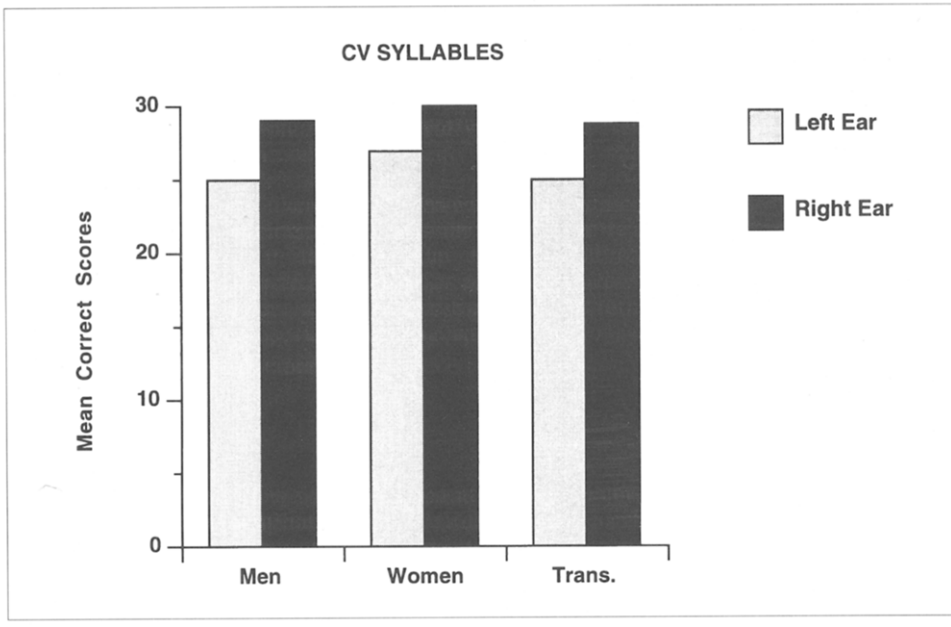

Fig. 1 – *Left- and right-ear performance in the perception of dichotic CV syllables.*

to report (yes or no) whether a target stimulus presented to both ears was identical to one in the preceding dichotic pair. One third of the target stimuli referred to sounds presented to the left ear, one third to sounds presented to the right, and one third had no dichotic referent. There was a one sec. delay between the dichotic stimulus; and an interstimulus (dichotic pair + target) interval of four sec. The procedure was similar to that reported in Cohen, Levy and McShane, 1989).

Results

An analysis of variance of Group (Men, Women, Transsexuals) × Ear (Left, Right) with repeated measures on the second factor was performed on the correct scores for each dichotic task. Results showed, for the three groups of subjects, an Ear effect indicating a right ear advantage for CV stimuli ($F = 8.272$; d.f. = 1, 31; $p < .05$) and for nonsense syllables ($F = 5.12$; d.f. = 1, 31; $p < .05$). The treatment of nonverbal dichotic material, on the other hand, suggested a more complex pattern of auditory asymmetry between the groups. The analysis revealed interactions showing a left ear advantage in treatment of melodies ($F = 6.16$; d.f. = 2, 31; $p < .05$) and 3T ($F = 6.871$; d.f. = 2, 31; $p < .05$) for men only. Post hoc Newman-Keuls tests (p's < 0.5) showed that the men's pattern of ear performances, a left ear advantage, differed significantly from that of transsexuals' in the case of melodies, and of women and transsexuals in the case of 3T. There were no differences between women and transsexual subjects in the nonverbal dichotic listening tasks. Figure 1, 2, 3, and 4 show dichotic listening performances for the three groups of subjects.

Discussion

In the present study, we have investigated the contribution of hormonal environment in auditory cerebral functional asymmetry. The men, women, and genetic male transsexuals who participated in this study all showed a right-ear advantage in the treatment of speech

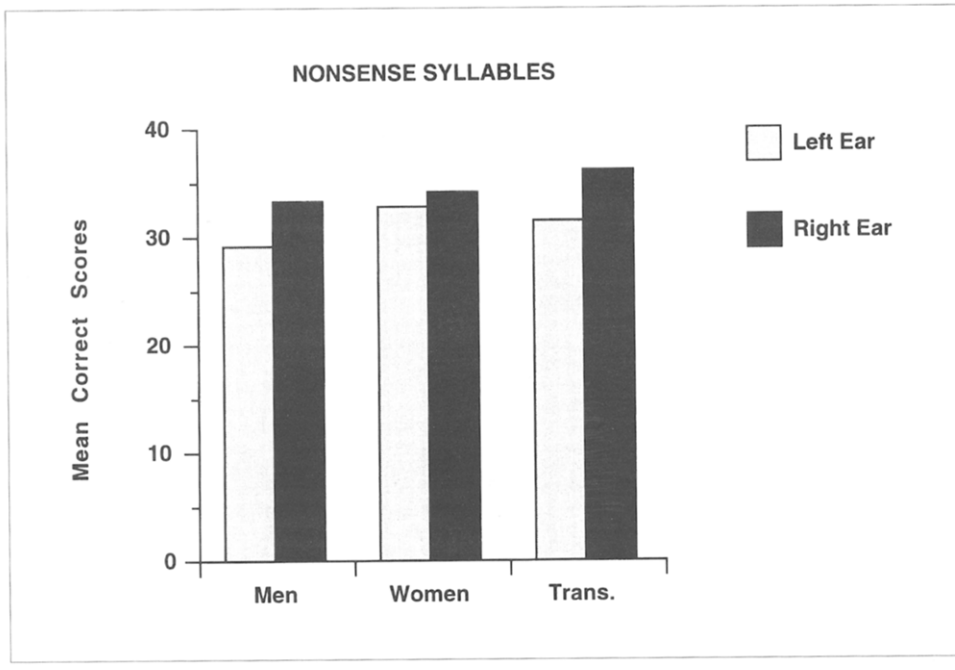

Fig. 2 – *Left- and right-ear performance in the perception of dichotic nonsense syllables.*

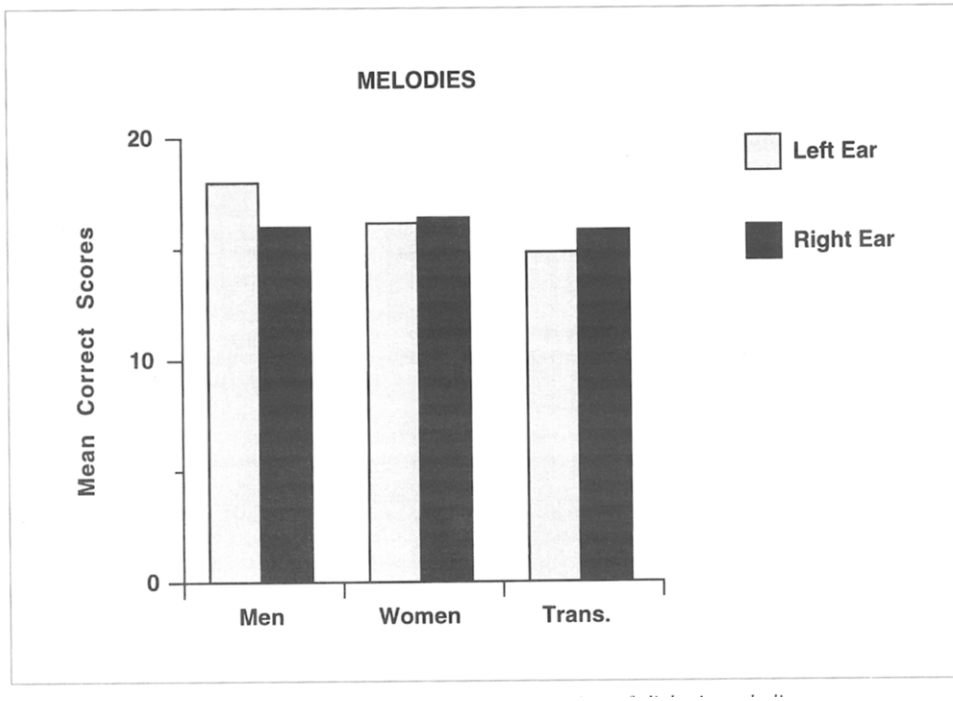

Fig. 3 – *Left- and right-ear performance in the perception of dichotic melodies.*

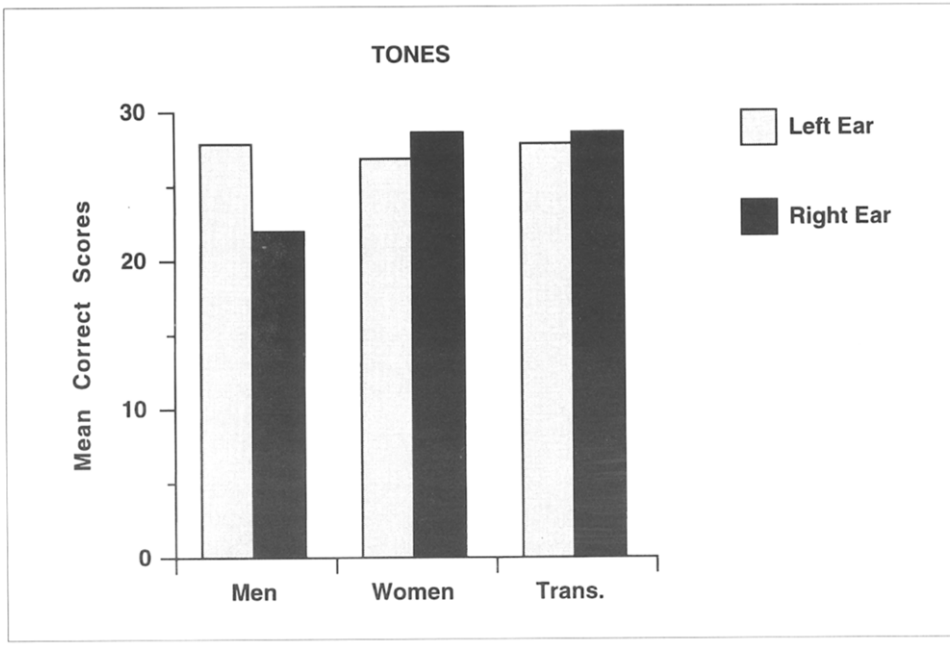

Fig. 4 – *Left- and right-ear performance in the perception of dichotic triple tones.*

information. Differences between groups were observed with respect to lateralization of non speech sounds where men, women and transsexuals showed different pattern of ear advantage for perception of melodies and triple tones. In these contexts, a significant left-ear advantage was revealed for men; no such pattern was present in women and transsexual subjects.

As such, the data on ear advantages showed that women and genetic transsexual males did not differ significantly in any of the four dichotic listening tasks. Moreover, differences occurred principally between men and transsexuals in the context of nonverbal tasks. This would suggest a possible hormonal involvement in the modulation of hemispheric specialization for nonspeech sounds in adults (see also Kimura, 1992, for a discussion of hormonal influences on brain organization and intellectual function).

It would be tempting to speculate that, for men, right hemispheric processes — inasmuch as left-ear performances reflect such processes — are preferentially affected by hormonal variations. Indeed, there is ample evidence from the animal literature that hormones may contribute importantly to the expression of sexually differentiated patterns of behavior as well as in determining morphogenesis of the cerebral cortex (e.g., Diamond et al., 1981; Glick, 1983; Hines and Shipley, 1984). For example, Diamond, Johnson and Ingham (1975) found that, in male rats, the right cerebral cortex was thicker than the left. These differences were present in the newborn and continued in varying degrees throughout the lifetime of the male rats. The greater thickness in the male right cortex compared to the left was supported by cell counts (McShane, Glaser, Greer et al., 1988). In addition, the presence of estrogen receptors during development of the cerebral cortex has been implicated in establishing the hemispheric asymmetrical pattern, cortical and subcortical, found in rats (Diamond, 1987; Sandhu, Cooke and Diamond, 1986) and in finches (e.g., Gurney and Konishi, 1980), Moreover, manipulations of hormonal levels in adult male rats appear to reverse the usual right-greater-than-left pattern of cortical dominance, supporting the hypothesis that gonadal hormones play a role in determining cortical laterality in some cortical regions (e.g., Pappas, Diamond and Johnson, 1989; Diamond, 1984).

A note of caution, however, is in order. Since it was not possible to test the transsexual subjects in this study in their eugonadal state, we cannot strongly conclude that patterns of hemispheric specialization are affected by hormonal variations. It could also be that other

factors, such as socialization (but see Meyer-Bahlburg, 1984) or genetic determinants of sexual differentiation, may be involved in the modulation of patterns of cerebral functional specialization and that hormonal correction has little or no effects on deviations from pattern observed for each biological sex.

There is evidence, however, that hormonal changes and reactions can occur in adults. It is already known that lower mammals have a sex-specific response of luteinizing hormone (LH) secreting to an estrogen stimulus of sufficient intensity and duration (e.g., McEwen, 1981). Females respond with an increase in LH secretion, while males show a decrease. More recently, Gooren (1986) has determined that the LH response to an estrogen stimulus is not sex-specific in humans and not permanently imprinted perinatally. In his study of genetic male and female transsexuals, all subjects were first tested before hormone therapy in a eugonadal state corresponding to their genetic sex and again following gonadectomy and treatment with cross-gender hormones. His results showed that, before any treatment, all transsexuals exihibited a LH response to estrogen administration appropriate to their biological sex. The same subjects showed the opposite response consequent with their reassigned sex (p. 589; see also Gooren, Rao, van Kessel et al., 1984). Such findings suggest that, in humans, the LH response may be related to the nature of the circulating sex steroids. From the results obtained in the present study, it is possible that changes in hormonal environment, as they are expressed in transsexuals, may have a selective modulatory effect on the direction of cerebral asymmetry in adult subjects. It may also be that one of the effects of hormonal therapy on our transsexual subjects is to alter, in some fashion, a testosterone range optimal for the expression of a particular ability or function. To our knowledge, it seems that differences between control male subjects and transsexual individuals in neuroendocrine response or hemispheric asymmetry can be partially explained by administration of gonad steorid hormones. In a more recent study with subjects showing gender dysphoria (female-to-male transsexual candidates, prior to any medical treatment and to surgical sex reassignment), Herman et al. (1993) showed that neither biological sex nor gender identity are sufficient factors to determine the pattern of hemispheric asymmetry (p. 269).

Given the important contribution of gonadal hormones in the sexual differentiation of a rather large repertoire of behaviors, it remains important to specify the extent of hormonal involvement in cognitive sex differences. But until we have a satisfactory integrative model of brain function it is difficult to know how biology interacts with behavior — how hormones affect complex responses such as ear advantages. A more complex interactional model is required to understand the nature of regional cerebral modulations in cognition that recognizes the multicontextual influences — biological, psychological, environmental — that affect central processes.

Acknowledgement. This work was supported by grants from UQAM, FCAR and Fonds de la Recherche en Santé du Québec. We thank Claude Braun for helpful criticism.

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